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V. Namasivayam, R. Günther

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Flexible Peptide-Protein Docking Employing PSO@Autodock

Vigneshwaran Namasivayam and Robert Günther

Institute of Biochemistry, Faculty of Biosciences, Pharmacy, and Psychology,
Universität Leipzig, Brüderstr. 34, 04103 Leipzig, Germany
E-mail: {vignesh, robguent}@uni-leipzig.de

In this paper we present the application of our recently developed docking program PSO@Autodock to screen a peptide library for the lethal factor of anthrax and to shed light on the application of the underlying scoring function for peptide-protein docking.

1 Introduction

Communication in biological systems occurs via specific molecular interactions. Thus, detailed knowledge of protein-ligand interactions might help to gain insight into fundamental events in the communication process of biological systems. Molecular docking methods have proven to be viable tools for studying the binding geometries and affinities of ligands to proteins. Current docking methods are designed for screening libraries of low molecular weight compounds. However, the majority of endogenous ligands are peptides. Though the development of methods to dock highly flexible ligands like peptides is evolving, the development of appropriate scoring functions is lagging behind.

We developed the molecular docking program PSO@Autodock¹ for fast flexible molecular docking. It is build upon AutoDock3 (AD3)², where the docking procedure is realized as multidimensional optimization. PSO@Autodock employs particle swarm optimization (PSO) techniques to find the optimal protein-ligand complex. In PSO, the locations, orientations and conformations of the ligands are represented as individual particles, which move through the search space similar to flocking birds. The *varCPSO*-ls algorithm of PSO@Autodock can efficiently screen high-dimensional search spaces. In this study we investigated the applicability of the underlying scoring function of AD3² for peptide-protein docking.

2 Data Preparation and Methods

For AD3 and PSO@Autodock, the protein-ligand complexes were prepared with AutoDockTools: Kollman charges were assigned for the proteins and Gasteiger charges for the ligand molecules. A grid box with a size of 90x90x90 points with a spacing of 0.375 Å was defining around the co-crystallized ligand. For GOLD (version 3.0, CCDC, Cambridge UK), the molecules were prepared using the MOE 2007.09 (CCG Inc., Montreal, Canada) and Amber89 charges were applied to the systems. Default parameters were used for AD3 and GOLD. For PSO@Autodock the cognitive and social parameters were set to 6.05. The dockings runs were stopped after 100,000 evaluations for the initial comparison study and after 500,000 evaluations for the peptide-protein dockings.

3 Flexible Peptide-Protein Docking Studies

We compared the performance of PSO@Autodock with the docking programs AD3 and GOLD. Thus, we screened a set of 10 protein complex structures with highly-flexible ligands (15 to 24 torsional angles). PSO@Autodock clearly outperforms the other docking programs. The average RMSD value of all the docked complexes is with 1.6 Å significantly lower than that obtained with AD3 or GOLD, which is above 3.0 Å in both cases (Table 1).

Complex	Torsions	PSO@Autodock	AutoDock3	GOLD3
1HRN	15	0.77	1.62	8.69
1CZI	16	4.39	5.71	3.03
1PPM	17	1.50	3.69	10.08
2FMB	20	3.84	4.60	6.72
3APR	21	0.66	2.87	11.54
1QRP	22	1.28	4.34	4.35
1WKR	22	0.74	1.28	11.68
3FIV	22	0.79	3.17	5.54
1HIV	23	0.85	2.98	2.77
1LYB	24	1.12	2.99	5.66

Table 1. Comparison of different docking methods (RMSD in Å).

Inspired by an experimental study³ we applied PSO@Autodock to dock a peptide library to the anthrax lethal factor (LF)³. LF is a zinc-dependent metalloproteinase secreted from *Bacillus anthracis* that cleaves the members of the MAPK kinase (MKK) family of intracellular signaling proteins. This action by LF rapidly blocks the signals that would normally recruit other immune cells to fight the infection.

Four X-ray crystal structures of LF in complex with small molecule inhibitors and peptides have been reported³. First, we performed a cross-docking study in which all ligands are docked on the four crystal structures of LF to investigate whether potential ligand induced changes in the protein structure affect the accuracy of the docking. Independent of the protein structure used the native conformation of the ligand is reproduced in all complexes. The docking on the complex structure with the peptide LF20 (KKVYPYPMEPT) 1pww.pdb³ predicts the ligands in all cases correctly with an RMSD < 2 Å (Fig. 1.a). Thus, we selected this complex for further studies.

A random sequence has been introduced in to the peptide library as a negative control as shown in Fig. 1.b. All peptides bind in the cavity region similar to the co-crystallized ligand in 1pww.pdb. Although the random sequence binds near the binding pocket, its affinity is predicted to be lower than the substrate sequences. This proves that the AD3 scoring function in PSO@Autodock can distinguish specific from non-specific peptides. However, it is difficult to differentiate between the binding strength of similar peptides. This is probably due to the limited accuracy of the AD3 scoring function², which has a residual error of 2.113 kcal/mol.

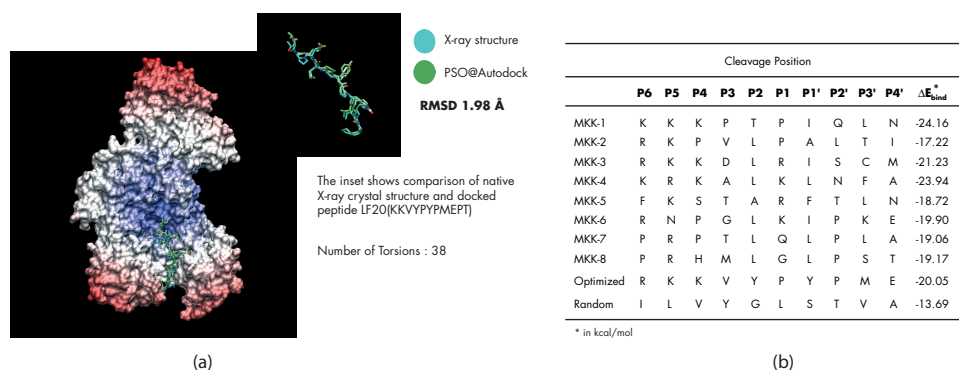


Figure 1. (a) X-ray crystal structure of lethal factor (1pww.pdb) in complex with peptide LF20 (KKVYPYPMEPT) (b) Peptide Library.

4 Concluding Remarks

PSO@Autodock can be applied for flexible peptide-protein docking studies. However, the scoring function currently implemented in PSO@Autodock is sufficient to discriminate between good binders and non-binders to a protein, but not accurate enough to predict the binding affinity correctly. Thus a novel scoring function has to be developed. A promising candidate for such a scoring function could follow the empirical approach of RosettaDock⁴.

Acknowledgments

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References

1. V. Namasivayam, R. Günther, *PSO@Autodock : A fast flexible molecular docking program based on swarm intelligence*, Chem. Biol. Drug. Des. **70**, 475, 2007.
2. G.M. Morris, D.S. Goodsell, R.S. Halliday, W.E. Hart, R. Belew, A.J. Olson, *Automated docking using a Lamarckian Genetic Algorithm and an empirical binding free energy function*, J. Comp. Chem. **19**, 1639, 1998.
3. B.E. Turk, T.Y. Wong, R. Schwarzenbacher, E.T. Jarrell, S.H. Leppla, R.J. Collier, R.C. Liddington, L.C. Cantley, *The structural basis for substrate and inhibitor selectivity of the anthrax lethal factor*, Nat. Struct. Mol. Biol. **11**, 60, 2004.
4. J.J. Gray, S. Moughon, C. Wang, O. Schueler-Furman, B. Kuhlman, C.A. Rohl, D. Baker, *Protein-Protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations*, J. Mol. Biol. **331**, 281, 2003.

